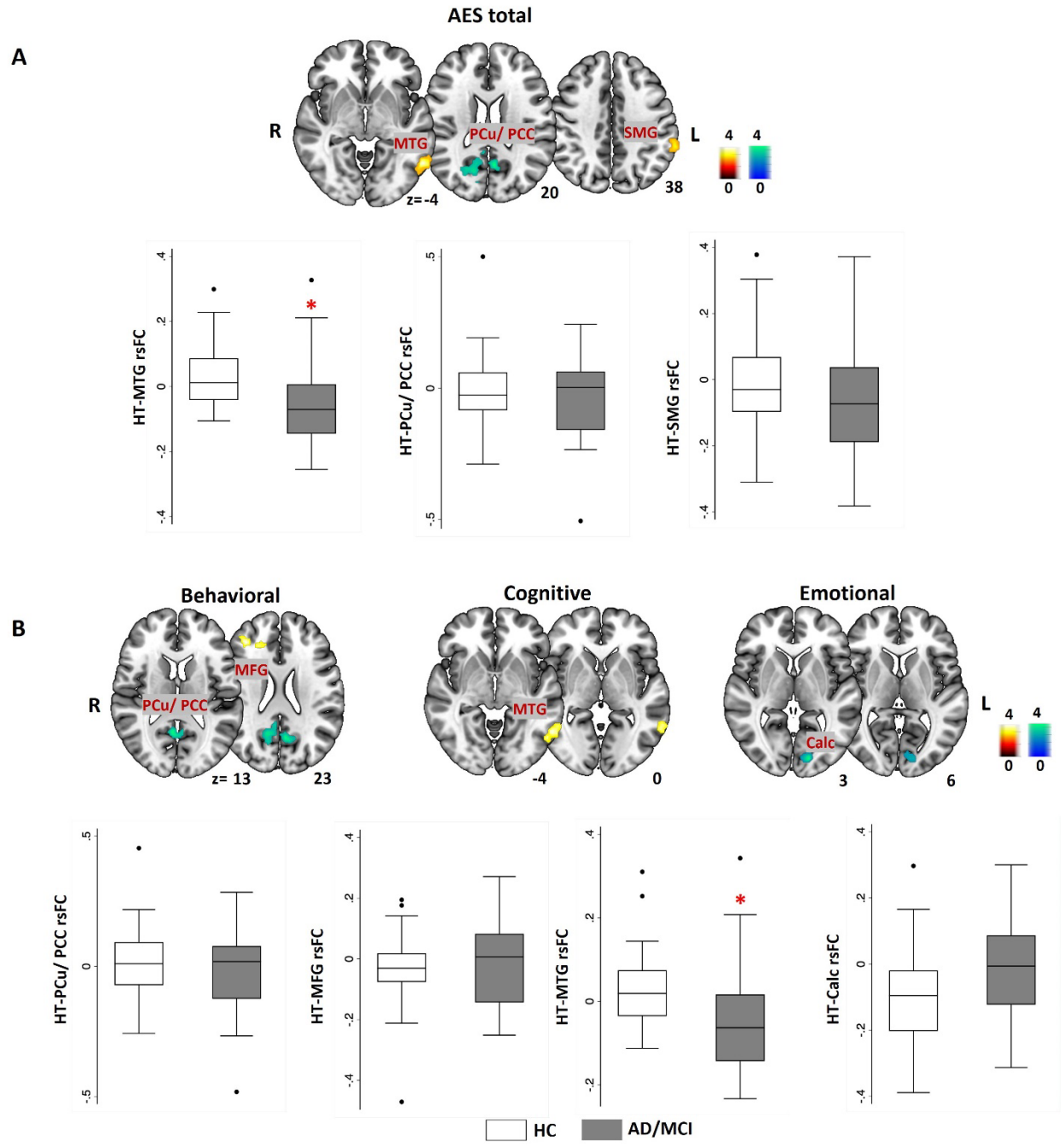
Supplementary Material

Hypothalamic Functional Connectivity and Apathy in People with Alzheimer's Disease and Cognitively Normal Healthy Controls

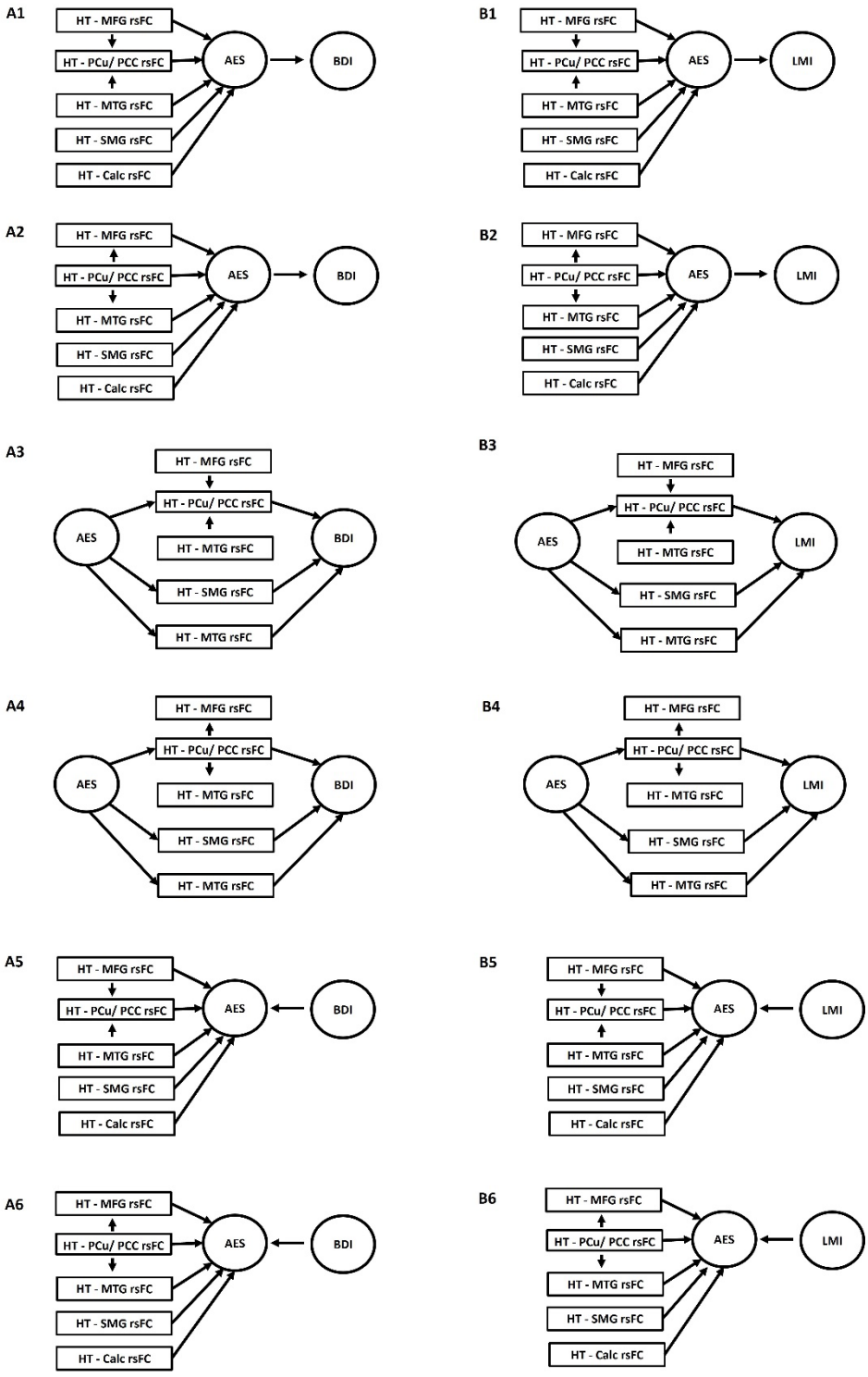
Supplementary Table 1. Correlation of AES apathy scores with clinical variables in AD/MCI and in HC.

	MMSE		**LMI**		**LMII**		**BDI-II**	
	r	p	r	p	r	p	r	p
AD/MCI								
AES Total	-0.54	0.004*	-0.16	0.441	0.06	0.772	0.66	<0.001*
Cognitive	-0.57	0.002*	-0.28	0.161	-0.01	0.946	0.62	<0.001*
Behavioral	-0.51	0.007*	-0.11	0.594	0.008	0.969	0.63	<0.001*
Emotional	-0.29	0.145	0.19	0.349	0.43	0.028*	0.69	<0.001*
HC								
AES Total	-0.14	0.509	-0.53	0.006*	-0.07	0.725	0.55	0.005*
Cognitive	-0.09	0.652	-0.51	0.009*	-0.07	0.683	0.58	0.002*
Behavioral	-0.16	0.443	-0.60	0.001*	-0.16	0.455	0.44	0.028*
Emotional	-0.12	0.553	-0.12	0.563	0.01	0.952	0.36	0.078

AD, Alzheimer's disease; MCI, mild cognitive impairment; HC, healthy controls; r, Pearson's partial correlation coefficient corrected for age, sex, and education; *p<0.05, MMSE, Mini-Mental State Examination; LMI, logical memory immediate; LMII, logical memory delayed; BDI, Beck Depression Inventory; AES, Apathy Evaluation Scale



Supplementary Figure 1. Hypothalamus rsFC (β) identified of whole-brain regression on AES (A) total score and (B) subscores in AD/MCI and HC. Each box plot shows the mean and SD of the mean. The clusters were shown on the top rows, with color bars indicating voxel t values (warm/cool: positive/negative correlation). *Two-sample t-test $p<0.05$ adjusted for age, sex, education, Mini-Mental State Examination, and Beck Depression Inventory-II scores; rsFC, resting state functional connectivity; AES, Apathy Evaluation Scale; AD, Alzheimer's disease; MCI, mild cognitive impairment; HC, healthy controls; HT, hypothalamus; MTG, middle temporal gyrus; PCu/PCC, precuneus/posterior cingulate cortex; SMG, supramarginal gyrus; MFG, middle frontal gyrus; Calc, calcarine cortex.



Supplementary Figure 2. Models assessed in path analyses. Models A1-6 examined the inter-relationships between hypothalamic rsFCs, apathy, and depression; and models B1-6 examined the inter-relationships between hypothalamic rsFCs, apathy, and memory. rsFC, resting state functional connectivity; AES, Apathy Evaluation Scale; HT, hypothalamus; MFG, middle frontal gyrus; PCu/PCC, precuneus/posterior cingulate cortex; MTG, middle temporal gyrus; SMG, supramarginal gyrus; Calc, calcarine cortex; BDI, Beck Depression Inventory; LMI, logical memory immediate

Supplementary Table 2. Fit indices of the models assessed in path analysis of AES total score, hypothalamic rsFCs, and BDI-II score.

	Model A1*	**Model A2**	**Model A3**	**Model A4**	**Model A5***	**Model A6**
Likelihood ratio						
χ^2	9.48	25.02	62.91	69.67	1.88	18.24
$p > \chi^2$	0.220	0.005	<0.001	<0.001	0.59	0.011
Population error						
RMSEA	0.07	0.16	0.31	0.28	0.00	0.17
90% CI, lower bound	0.00	0.08	0.24	0.22	0.00	0.08
90% CI, upper bound	0.19	0.24	0.38	0.35	0.19	0.27
Baseline comparison						
CFI	0.97	0.87	0.52	0.56	1.00	0.90
Size of residuals						
SRMR	0.06	0.10	0.17	0.19	0.02	0.09
Information criteria						
AIC	387.21	406.75	444.64	459.41	375.61	395.97
BIC	415.81	439.44	477.33	500.27	400.13	424.57

*Model with good fit. A good model fit is reflected in indices including χ^2 $p>0.05$, root mean square error of approximation (RMSEA)$\leq$0.08, standardized root mean squared residual (SRMR)$\leq$0.08, and comparative fit index (CFI)$\geq$0.90 [1,2]. We also included Akaike's information criterion (AIC) and Bayesian information criterion (BIC) values in the table, both with a smaller value indicating better fit of the model. AES, Apathy Evaluation Scale; rsFC, resting state functional connectivity; BDI, Beck Depression Inventory

Supplementary Table 3. Fit indices of the models assessed in path analysis of AES total score, hypothalamic rsFCs, and LMI score.

	Model B1	Model B2	Model B3	Model B4	Model B5*	Model B6
Likelihood ratio						
χ^2	23.07	38.62	47.47	54.23	4.85	18.56
$p > \chi^2$	0.002	<0.001	<0.001	<0.001	0.183	0.010
Population error						
RMSEA	0.20	0.23	0.26	0.24	0.10	0.17
90% CI, lower bound	0.11	0.15	0.19	0.17	0.00	0.08
90% CI, upper bound	0.29	0.20	0.34	0.30	0.27	0.27
Baseline comparison						
CFI	0.81	0.72	0.63	0.66	0.98	0.88
Size of residuals						
SRMR	0.12	0.15	0.16	0.18	0.03	0.11
Information criteria						
AIC	455.49	475.03	483.88	498.65	433.27	450.97
BIC	484.09	507.72	516.57	539.51	457.78	479.58

*Model with satisfactory fit. A good model fit is typically assessed with indices including χ^2 $p>0.05$, root mean square error of approximation (RMSEA)$\leq$0.08, standardized root mean squared residual (SRMR)$\leq$0.08, and comparative fit index (CFI)$\geq$0.90 [1,2]. We also included Akaike's information criterion (AIC) and Bayesian information criterion (BIC) values here in the table, both with a smaller value indicating better fit of the model. AES, Apathy Evaluation Scale; rsFC, resting state functional connectivity; LMI, logical memory immediate

Supplementary Table 4. Demographic and clinical characteristics of HC and amyloid-verified AD.

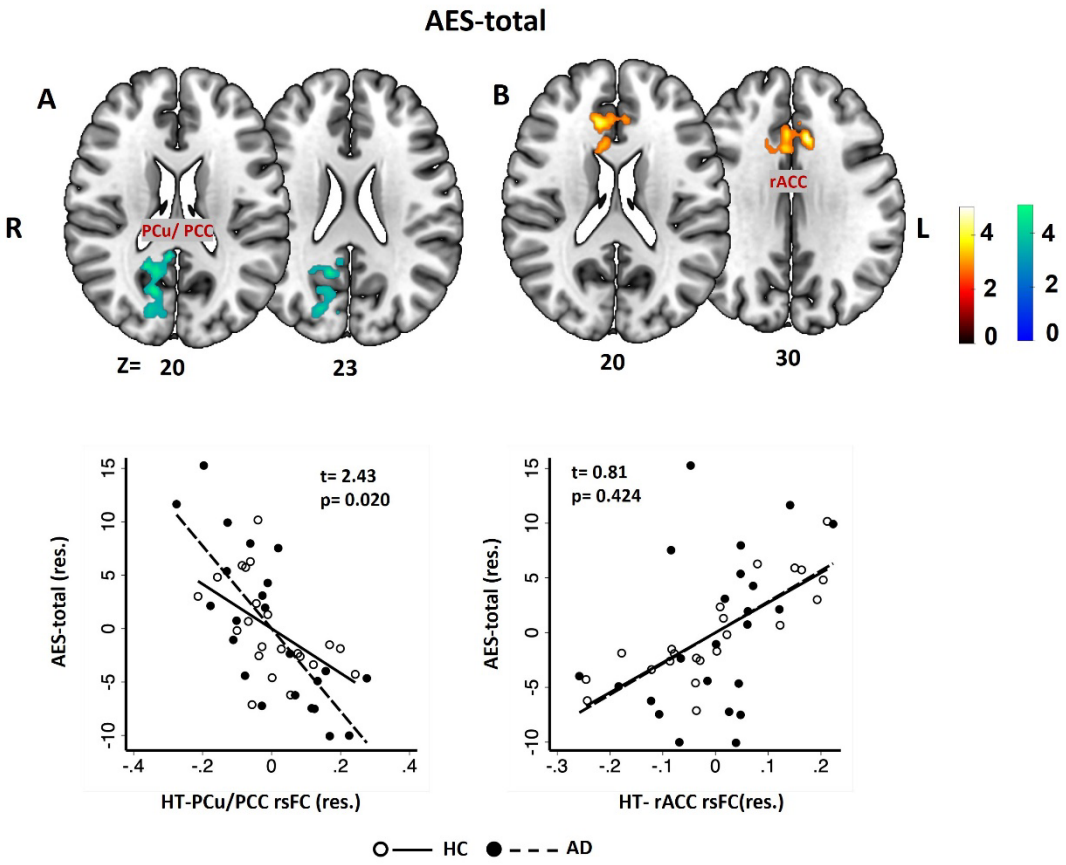
	HC (n=22)	AD (n=23)	$t/\chi^2/z$-, p
Age (y) [a]	72.3 ± 4.1	75.1 ± 5.5	1.97, 0.055
Sex (male/female) [b]	9/13	11/12	0.22, 0.641
Education (y) [a]	17.1 ± 2.0	16.2 ± 2.3	1.61, 0.113
CDR	0	1.0 (n=20) 2.0 (n=3)	---
MMSE [a]	29.8 ± 0.3	21.0 ± 6.2	6.75, <0.001*
LMI (immediate) [c]	22.0 ± 4.8	6.8 ± 3.8	11.6, <0.001*
LMII (delayed) [c]	18.8 ± 5.7	0.7 ± 1.6	14.5, <0.001*
BDI-II [c]	4.4 ± 4.7	8.2 ± 5.3	2.56, 0.014*
AES total [c]	24.6 ± 5.5	31.7 ± 13.7	2.24, 0.030*
AES cognitive [c]	11.0 ± 2.4	13.9 ± 6.6	1.92, 0.062
AES behavioral [c]	6.7 ± 1.7	9.3 ± 3.8	2.94, 0.005*
AES emotional [c]	3.1 ± 1.1	3.2 ± 1.5	0.09, 0.924

*$p<0.05$; [a] two-sample t-test, [b] χ^2-test, [c] two-sample Wilcoxon rank-sum (Mann-Whitney) test; HC, healthy controls; AD, Alzheimer's disease; CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination; LMI, logical memory immediate; LMII, logical memory delayed; BDI, Beck Depression Inventory; AES, Apathy Evaluation Scale

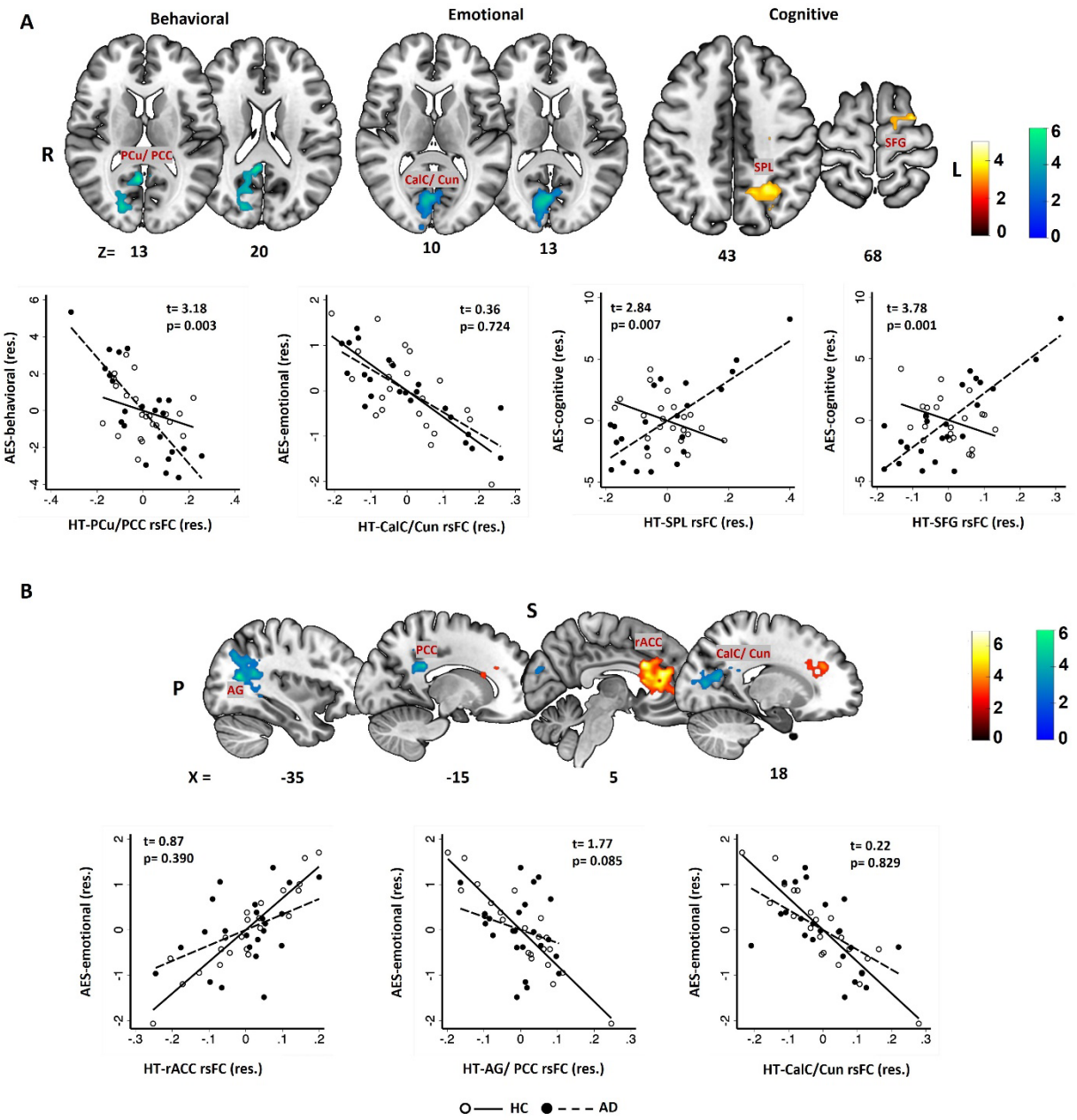
Supplementary Table 5. Correlation of AES apathy scores with clinical variables in amyloid-verified AD and HC.

	MMSE		LMI		LMII		BDI-II	
	r	p	r	p	r	p	r	p
Amyloid positive AD (n=23)								
AES Total	-0.56	0.011*	-0.30	0.195	-0.25	0.285	0.68	0.013*
Cognitive	-0.58	0.007*	-0.42	0.067	-0.25	0.289	0.67	0.001*
Behavioral	-0.49	0.027*	-0.12	0.625	0.19	0.413	0.60	0.004*
Emotional	-0.40	0.078	-0.17	0.483	-0.14	0.565	0.77	<0.001*
HC (n=22)								
AES Total	-0.23	0.345	-0.64	0.006*	-0.18	0.495	0.55	0.014*
Cognitive	-0.28	0.245	-0.61	0.009*	-0.18	0.476	0.58	0.009*
Behavioral	-0.09	0.717	-0.62	0.008*	-0.11	0.663	0.40	0.085
Emotional	-0.24	0.329	-0.47	0.059	-0.26	0.306	0.51	0.024*

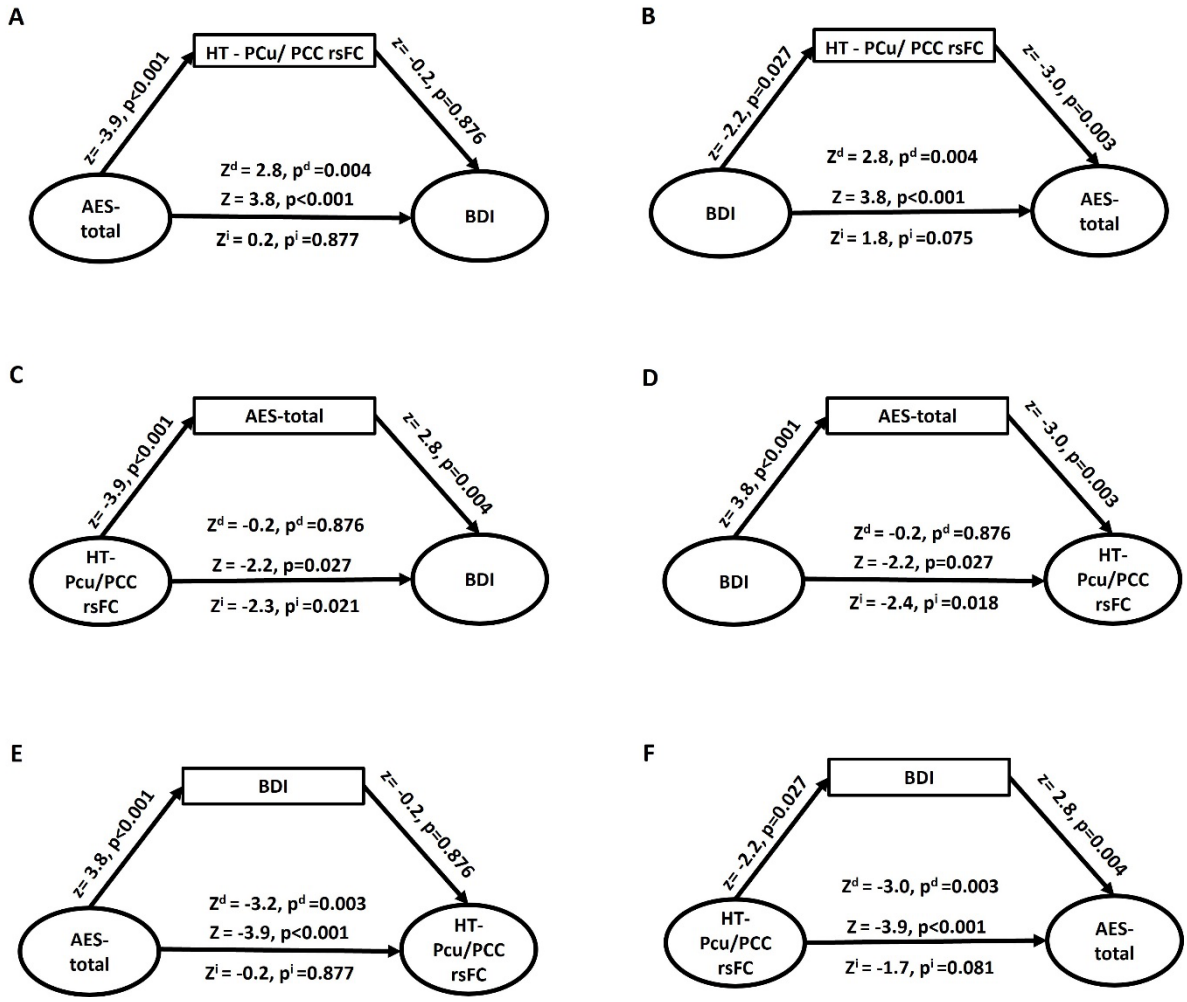
r, Pearson's partial correlation coefficient corrected for age, sex, and education; *p<0.05, MMSE, Mini-Mental State Examination; LMI, logical memory immediate; LMII, logical memory delayed; BDI, Beck Depression Inventory; AES, Apathy Evaluation Scale; HC, healthy controls; AD, Alzheimer's disease



Supplementary Figure 3. Whole-brain multiple regression of HT rsFC with AES total in (A) amyloid-positive AD and (B) HC. Color bars indicate voxel T values (warm/cool: positive/negative correlation). The bottom row shows the scatterplots of AES-total versus extracted mean HT rsFCs with regression lines shown separately for HC and AD. Note that the data represent values in residuals (res.) and the t- and p-values are of the tests of the regression slopes in HC versus AD. For all analyses, we controlled for age, sex, education, MMSE, and BDI-II. HT, hypothalamus; rsFC, resting state functional connectivity; AES, Apathy Evaluation Scale; AD, Alzheimer's disease; HC, healthy controls; PCu, precuneus; PCC, posterior cingulate cortex; rACC, rostral anterior cingulate cortex; MMSE, Mini-Mental State Examination; BDI, Beck Depression Inventory



Supplementary Figure 4. Whole-brain multiple regression of HT rsFC with AES behavioral, cognitive, and emotional subscores across (A) amyloid-positive AD and (B) HCs. Color bars indicate voxel T values (warm/cool: positive/negative correlation). The bottom rows show the scatterplots of AES subs-cores versus extracted mean HT rsFCs with the regression lines shown separately for HC and AD. Note that the data represent values in residuals (res.) and the t- and p-values are of the slope tests of HC versus AD for the corresponding correlations. For all analyses, we controlled for age, sex, education, MMSE, and BDI-II. HT, hypothalamus; rsFC, resting state functional connectivity; AES, Apathy Evaluation Scale; AD, Alzheimer's disease; HC, healthy controls; PCu, precuneus; PCC, posterior cingulate cortex; Calc/Cun, calcarine cortex/cuneus; SFG, superior frontal gyrus; SPL, superior parietal lobule; AG, angular gyrus; rACC, rostral anterior cingulate cortex; MMSE, Mini-Mental State Examination; BDI, Beck Depression Inventory



Supplementary Figure 5. Mediation models of AES-total, BDI, and HT-PCu/PCC rsFC in amyloid positive AD. z = total effect, z^d = direct effect, z^i = indirect/mediated effect. Model C and model D show compete mediation [3,4]. HT, hypothalamus; rsFC, resting state functional connectivity; AES, Apathy Evaluation Scale; AD, Alzheimer's disease; PCu, precuneus; PCC, posterior cingulate cortex; BDI, Beck Depression Inventory

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